Autoimmune haemolytic anaemia associated with COVID-19 infection

Among patients with SARS-CoV-2 infection (also known as COVID-19), pneumonia, respiratory failure and acute respiratory distress syndrome are frequently encountered complications.[1] Although the pathophysiology underlying severe COVID-19 remains poorly understood, accumulating evidence argues for hyperinflammatory syndrome causing fulminant and fatal cytokines release associated with disease severity and poor outcome.[2] However, the spectrum of complications is broader and includes among others various auto-immune disorders such as autoimmune thrombocytopenia, Guillain–Barré and antiphospholipid syndrome.[3–5] In this report we describe seven patients from six French and Belgian Hospitals who developed a first episode of autoimmune haemolytic anaemia (AIHA) during a COVID-19 infection.

Patient characteristics are detailed in Table I. Briefly, median age was 62 years (range, 61–89 years), and all patients presented with risk factors for developing a severe form of COVID-19 such as hypertension, diabetes and chronic renal failure. All patients had both a positive oropharyngeal swab for SARS-CoV-2 and typical images of COVID-19 infection on chest computed tomography scans (25–75% extension). Three patients were admitted in an intensive care unit but only one required invasive ventilation. Treatment for COVID-19 infection differed according to the standards of each centre. Thus, three patients received hydroxychloroquine, in association with azithromycin for two of them, and one patient received lopinavir and ritonavir.

The median time between the first COVID-19 symptoms and AIHA onset was nine days (range 4–13 days), and haemoglobin level decreased by more than 30 g/l in all cases. Median haemoglobin level at the time of AIHA diagnosis was 70 g/l (range 3·8–10·8), and all patients presented with marked haemolysis signs. Direct antiglobulin test (DAT) was positive in all cases either for IgG (n = 2), for C3d (n = 2), or for both IgG and C3d (n = 3). Anti-erythrocyte antibodies were warm antibodies in four cases (two of IgG specificity and two IgG + C3d) and cold agglutinins in three cases (two of C3d specificity and one IgG + C3d). At the time of AIHA onset, all patients had elevated markers of inflammation (i.e. fibrinogen, D-dimers and C-reactive protein).

Interestingly, among the patients with warm antibodies, two patients were known for stable untreated Binet stage A chronic lymphocytic leukaemia (CLL); an IgG kappa monoclonal gammopathy of undetermined significance was demonstrated in a third one. In 2/3 patients with cold agglutinin, systematic lymphocyte immunophenotyping demonstrated the presence of a monotypic B lymphoid population with a phenotype compatible with marginal zone lymphoma (MZL). The third one was diagnosed with prostate cancer.

AIHA management included corticosteroids for five patients, and red blood cells infusions for two. Even if the follow-up is still short, three patients receiving corticosteroids were evaluable for response of AIHA. Two patients reached partial response defined by haemoglobin level >100 g/l along with an increase of 20 g/l at least seven days after an infusion with red blood cells.

Corticosteroid failure lead to rituximab injection in the third case (patient #6), and one responding patient is scheduled to receive rituximab because of a MZL clone (patient #3).

At the time of last follow-up, all patients were alive and had at least partly recovered from COVID-19.

To conclude, we report seven cases of warm and cold AIHA associated with COVID-19 disease, all of them occurring after the beginning of the symptoms of the infection and within a timeframe compatible with that of the cytokine storm. Four out of the seven patients had indolent B lymphoid malignancy either already known or discovered because of the haemolytic episode. AIHA is a classical complication of both CLL and MZL,[6,7] and viral infections are known to trigger autoimmune cytopenias.[8] Whether the presence of an underlying malignant B lymphoid clone facilitated the onset of AIHA is unknown. Nonetheless, these observations argue for systematically investigating for the presence of a lymphoid clone in patients presenting with COVID-19 infections and autoimmune cytopenias.

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Author contributions

GL, AQ and FC designed the research study, analyzed the data and wrote the paper. MB, JS, CJ, DR, FM, AM, TB, GD and AD contributed to conception, patient enrollment and data collection.

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Table I. Characteristics of seven patients with autoimmune haemolytic anaemia after the onset of COVID-19.

Patient	Age	Gender	Comorbidity	CT-scan*	Oropharyngeal swab (tested by PCR)	Haemoglobin (g/l)	Reticulocyte count (10^9/l)	Lymphocyte count (10^9/l)	Lactate dehydrogenase (U/l)	Haptoglobin (g/l)	DAT specificity	Optimum temperature	Day between COVID-19 symptoms and AIHA	Related pathology	AIHA treatment	Response
#1	61	M	Hypertension, chronic renal failure	Moderate	Positive	60	477	250	1000	<0·1	IgG + C3d	warm	13	CLL	Steroids	Ongoing
#2	89	F	Hypertension, chronic renal failure, atrial fibrillation	Mild	Positive	84	103	1·7	598	<0·1	IgG + C3d	warm	7	MGUS	Steroids	Ongoing
#3	62	F	Hypertension, cirrhosis	Severe	Positive	108	101	1·3	357	<0·1	C3d	cold	4	MZL†	1. Steroids 2. Rituximab	PR Planed
#4	69	F	Obesity	Moderate	Positive	38	215	5·9	2610	<0·1	IgG + C3d	cold	10	MZL	Steroids	PR
#5	61	M	Hypertension, chronic renal failure, diabetes, hypercholesterolaemia	Mild	Positive	72	145	3	807	0·8	C3d	cold	11	Prostate cancer	RBC infusion	Ongoing
#6	61	M	Diabetes	Severe	Positive	70	155	1·2	1800	<0·1	IgG	warm	9	None	1. Steroids 2. Rituximab‡	Failure Ongoing
#7	75	M	Diabetes, hypercholesterolaemia, cardiopathy, obesity, chronic obstructive bronchopneumopathy	Moderate	Positive	71	98	108	2000	<0·1	IgG	warm	6	CLL	RBC infusion	Ongoing

CT, computed tomography; PCR, polymerase chain reaction; DAT, direct antiglobulin test; AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; MGUS, monoclonal gammopathy of undetermined significance; MZL, marginal zone lymphoma; RBC, red blood cells; PR, partial response.

*Degree of involvement of the lung was classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%).

†MZL B cell clone was detected in the bone marrow.

‡Patient 6 received rituximab injection because of corticosteroid failure.

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